REMARKS

In overview, a first Office Action issued in connection with the above-identified patent application on December 9, 2004 ("First Office Action"). Applicants responded with an amendment and response, filed March 9, 2005 ("March 9, 2005 Response"). Applicants have now considered the office action dated August 8, 2005, and subsequently re-mailed at the initiative of the Office, August 15, 2005 (the "Second Office Action").

Applicants thank Examiner Nashed for courtesies extended to Applicants' representative, the undersigned, during a telephonic discussion regarding the instant claims, on November 18, 2005.

Applicants also kindly ask the Office to note the attorney docket number for the instant application, *i.e.*, 19459-006US1 and not that currently used by the Office, and to ensure that the Office's records are updated in respect of the same.

Amendments to the Specification

Applicants amend the title of the instant application to more closely reflect the subject matter claimed therein and currently under examination.

Applicants also amend various portions of the specification to correct minor errors of a typographical nature, and to insert SEQ ID NOs in the manner requested by the Examiner.

In particular, Applicants amend the header to Appendix 1, on page 49 of the specification to more particularly describe the structure whose coordinates are contained therein. Since the structure is unchanged by any characterization thereof, and since the accuracy of the characterization can be readily confirmed by one of ordinary skill in the art, no new matter is introduced by such amendment, and entry thereof is respectfully requested.

Applicants draw the Examiner's attention to further discussion of the amendments that pertain to SEQ ID NOs, hereinbelow.

Since none of these amendments introduces new matter into the instant specification, entry thereof is proper, and is respectfully requested.

Amendments to the Claims

Applicants cancel claims 45, 47, 48, 138, 143, 149, 151, 152, and 154.

Applicants amend claims 44, 136, and 139 to recite an estrogen α complex, a limitation previously found in claim 45.

Applicants also amend claim 44 to introduce material previously found in claims 48, 143, and 149, all of which previously depended therefrom.

Applicants amend claim 46 to correct its dependency.

Applicants amend claim 136 to introduce material previously found in claims 138 and 152, depending therefrom, as well as from claim 48.

Applicants amend claim 139 to introduce material previously found in claims 152 and 143.

Applicants amend claim 142 to incorporate a limitation previously found in claim 48.

Applicants amend claims 44, 136, 150 and 153 to recite a fragment of a GRIP1 peptide, support for which is found in the specification as filed at page 40, line 31.

Applicants introduce new claim 155, reciting the cocrystal of claim 44 having resolved atomic structural coordinates presented in Appendix 1.

Accordingly, no new matter is introduced by the variuos amendments to the claims, and therefore entry thereof is respectfully requested.

Sequence Listing/Objections to Specification and Claims

The Examiner has objected to the specification for allegedly failing to comply with 37 C.F.R. § 1.821(d). In essence, the Examiner states that either sequences set forth in the "Sequence Listing" are discussed in the specification and claims without use of a sequence identifier, or that sequence(s) referenced in the specification are not also in the "Sequence Listing" and therefore that a replacement "Sequence Listing" must be filed and that such sequences should be given sequence identifiers. Applicants again disagree with the Examiner's reasoning in connection with certain terms, both for reasons stated in the March 9, 2005 Response, and for additional reasons discussed hereinbelow.

Nevertheless, Applicants have amended the specification in certain places where it is believed that doing so would be consistent with the rules for sequences cited by the Examiner. Such places are the various references in which a specific instance, presented in the Sequence Listing, is referred to in the specification.

The Examiner's references to parts of the specification and claims encompass terms such as "ERα", "estrogen receptor α", "NR Box", and "GRIP1". In many — if not most — of the instances of these terms, there is no intent to refer to a specific sequence. Indeed, from such context, it is clear that the reference is to a generic construct, or to a class of molecules, any member of which would have the referenced property or could be equivalently referenced.

For example, references to "ERα", "estrogen receptor α" and other similar designations, encompass many family members, as the Examiner likely appreciates. A copy of an excerpt from a recent text, *The Nuclear Receptor FactsBook*, listing exemplary family members is attached hereto for the Examiner's convenience. Applicants did not intend to limit their disclosure to a particular family member, but instead consistently referred to estrogen receptor α in generic terms. Furthermore, since those receptors have been identified by *name* only, and *not* by "a string of particular bases or amino acids", an entry in the Sequence Listing is not required under these circumstances. Applicants again respectfully draw the Examiner's attention to MPEP § 2422.03 which explains just this circumstance:

> In those instances in which prior art sequences are only referred to in a given application by name and a publication or accession reference, they need not be included as part of the "Sequence Listing," unless an examiner considers the referred to sequence to be "essential material," per MPEP § 608.01(p).

Since the Examiner has not asserted that the items in question are essential material, it is acceptable to refer to such entities in the specification without use of sequence identifiers. This is also the case because the entities are referenced by name not sequence, and because no corresponding sequence is provided in the Sequence Listing. Conversely, the Office cannot now require Applicants to provide a replacement Sequence Listing because the referenced molecules have not been represented by sequence in the first place, and to require that a particular sequence

be used would be forcing Applicants to limit their disclosure (by forcing particular generic terms to be associated with specific sequences) in a manner that was clearly not intended.

As the Examiner noted in the Second Office Action, when confronted with the first articulation of the instant objection (in the First Office Action) and in an effort to comply with the Examiner's request, Applicants amended the specification and claims in various places in the March 9, 2005 Response where compliance with the rules for sequence listings had been supposedly lacking. Those amendments included amendments to the header to Appendix 1, and the header to Appendix 2, at respectively pages 49 and 137 of the specification as filed (March 9, 2005 Response at pages 2–3). However, in the Second Office Action, the Examiner states that "the amendment to page 49 fails to overcome the objection with regard Appendix I and II [*sic*]" (Second Office Action at page 2, bottom). Applicants do not understand this statement: the headers to both Appendices 1 and 2 were amended to include sequence identifiers in the March 9, 2005 Response in a manner that Applicants believe would be clear to one of ordinary skill in the art and would comply with the Examiner's request. Nevertheless, Applicants readily appreciate that the structure in Appendix 1, being a dimer of two ternary complexes, is harder to describe than would be a crystal of a single species. Accordingly, and in a further effort to more fully describe that structure, Applicants again amend the header to Appendix 1 herein.

Notwithstanding the instant amendment, if Applicants understand the Examiner's reference to the structures in Appendices 1 and 2 to mean that, wherever, *e.g.*, an estrogen receptor α, is referenced in the specification, a sequence identifier for one of the sequences whose structure is found in the Appendices must be inserted, then Applicants believe such a request to be improper. As discussed hereinabove, references in the specification to, *e.g.*, an "estrogen receptor α," are intended to be generic; the structures in the Appendices are, of course, include specific examples of that general class of receptors. To insert throughout the specification specific sequence identifiers for the structures in the Appendices would be tantamount to limiting Applicant's disclosure to a particular embodiment. The Office cannot require Applicants to limit their entire disclosure in this manner.

Similar comments apply to the Examiner's objections to claims 46, 48, 138, and 143, all of which except claim 46 have been cancelled herein. Accordingly, Applicants respectfully request that the objection to claim 46 be removed.

In respect of claims 137 and 142, for which the Examiner's objection stands unmodified in the Second Office Action, Applicants respectfully point out that sequence identifiers were introduced in the March 9, 2005 Response. Accordingly, Applicants respectfully request that the objection as it pertains to claims 137 and 142 also be removed.

Accordingly, Applicants believe that no further amendments to the specification and claims are required, and therefore ask that the objection of record be removed.

REJECTIONS OF THE CLAIMS

After entry of the instant amendment, claims 1-25, 29-35, and 39-44, 46, 49-137, 139-142, 144-148, 150, 153, and 155 are pending in the instant application. Claims 1-25, 29-35, 39-43, 49, 51-135, 140, and 141 are withdrawn from consideration.

Claims 44, 46, 50, 136, 137, 139, 142, 144-148, 150, and 153 are therefore now under examination and stand rejected under one or more grounds. Claim 155 is newly presented herein.

Rejections under the "written description" requirement of 35 U.S.C. § 112(¶1)

The Examiner has rejected claims 44-48, 50, 136-139, and 142-154 as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) … had possession of the claimed invention." (Second Office Action at pages 2-3.) Claims 45, 47, 48, 138, 143, 149, 151, 152, and 154 are cancelled herewith. Applicants traverse with respect to the remaining claims rejected under this section.

With regard to claims 44, 46, 50, 142, 144-147, and 150, drawn to various embodiments of cocrystals comprising an estrogen receptor ligand binding domain, an agonist, and a molecule bound to the coactivator binding site, the Examiner states in the Second Office Action that Applicants' specification "does not provide any correlation between the primary structure of a protein and the crystallization conditions to be used". Applicants respectfully point out that this

articulation is more akin to an allegation of lack of enablement (separately addressed herein), rather than an allegation of a lack of written description and therefore believe that it is improper. Nevertheless, in an effort to be responsive, Applicants respectfully point out that the 'correlation' desired by the Examiner is not a "requirement" for written description support of the instant claims. Applicants have described how a representative claimed complex has been crystallized. As is further discussed hereinbelow, that description provides a starting point to one of ordinary skill in the art to obtain crystals of other structures within the scope of the claim, without undue experimentation.

Applicants note that the Examiner's previous rejection under the same paragraph was based on an assertion that "Applicants have provided only a single representative species … and that the specification fails to describe … any identifying structural characteristics or properties other than their composition, which fails to impart a high predictability of structure." (First Office Action at page 4). Applicants responded by demonstrating that Applicants' specification is replete with descriptions of the identifying characteristics of each component (receptor, agonist, and coactivator) of the crystal, as well as the manner in which the components bind to one another. (March 9, 2005 Response, pages 31-33). Accordingly, Applicants believe that those remarks directly addressed the alleged lack of written description, and therefore believe that it is improper for this rejection to be maintained on the alternative grounds expressed in the Second Office Action. Applicants additionally respectfully point out that the Examiner has not given any basis for deeming Applicants' March 9, 2005 Response to be "unpersuasive" but instead has articulated a newly phrased rejection, different in kind from the first. Does he discount the extensive description in Applicants' specification, as referenced in the March 9, 2005 Response, at pages 31-33? If not, some weight should be accorded it; if he does, then some specific explanation should be offered in place of a rearticulation on new grounds.

Furthermore, the Examiner's reasoning, as it applies to the different crystallization conditions applicable to "crystallization of the same protein with one agonist and one antagonist at page 36 [*sic*]" (Second Office Action at page 3) is faulty as it applies to the instant claims. Assuming the Examiner actually refers to page 37 of the specification as filed, wherein

conditions for obtaining two crystals are described, the Examiner is wrong in his characterization of the specification. First, lines 4-17 of page 37 of the specification describe crystallization of the "DES-hERα-GRIP1 NR Box II peptide complex." This is a *ternary* complex, having three components: a portion of an estrogen receptor (hERα), an agonist (DES), and a coactivator (GRIP1 NR Box II peptide). This complex is thus representative of Applicants' claims under examination herein. By contrast, the crystals described at lines 18-30 of page 37 of Applicants' specification are of the "hERα LBD complexed to OHT". This latter complex is thus a *binary* complex, having only two components: a portion of an estrogen receptor (hERα), and an antagonist (OHT). It is not surprising that the crystallization conditions employed for each are different, therefore, and the fact that they are has no bearing whatsoever on Applicants' claims since the claims are not drawn to the second — binary — type of complex. This distinction was pointed out by Applicants in their March 9, 2005 Response, at pages 34-35. Is it possible that the Examiner overlooked this fact?

Regarding claims 136, 137, 139, 148, and 153, drawn to an isolated and purified complex of an estrogen receptor ligand binding domain, an agonist, and a coactivator, and various embodiments thereof, the Examiner alleges that since such claims read on "all possible [such] purified and isolated composition[s] … in solution, vapor, amorphous precipitate, or crystalline form" and that since such claims read on crystalline forms, the foregoing grounds for rejection are applicable. Applicants again disagree. In particular, Applicants' specification shows how to obtain isolated and purified complexes, even prior to obtaining crystals. Accordingly, whatever the content of Applicants' crystallography data, Applicants have shown how to obtain such an isolated complex in its own right, regardless of whether it has been crystallized. Furthermore, Applicants have never understood the Office to articulate the view that a claim to composition of matter was lacking a proper written description because all possible phases of such a composition were not described. On the contrary, Applicants take the position (March 9, 2005 Response, page 33, last paragraph), that bringing about a phase change of a material is within the capability of one of ordinary skill in the art. Furthermore, even if it is conceded (which Applicants do not) that Applicants have not described with requisite certainty how to obtain

crystalline forms of the claimed complexes, a claim is not unpatentable because a small number of embodiments are not described.

Furthermore, Applicants respectfully point out that, with the amendments presented herein and in an effort to facilitate a swift allowance rather than to concede that the claims prior to amendment lacked support commensurate in scope with their breadth, much of the claims' breadth to which the Examiner took exception has been removed.

Finally, the Examiner's rejection of claims 44-48, 50, 136-139, and 142-154 under the written description requirements of 35 USC § 112 (first paragraph) takes no account of the varying scope of Applicants' claims and is phrased as if only to consider the limitations of independent claims 44 and 136 even though the rejections refer equally to all claims under examination. For example, nowhere has the written description support of the limitations of the various claims depending from claims 44 and 136 been individually addressed. Applicants respectfully submit that the rejection of record cannot apply with equal force to all claims so rejected and thus the dependent claims can only stand rejected as being dependent upon a rejected base claim, and not otherwise on the merits, without some clearly articulated reasoning why claims of successively narrowing scope are not also fully described. Therefore, on this basis, Applicants assert that the rejection has not been properly formulated, at least as it applies to claims 45-48, 50, 137-139, and 142-154. Applicants also respectfully request that the Examiner now reconsider the rejection under the written description requirement of 35 U.S.C. § 112(¶1) in light of the amendments to the claims presented herein as well as the foregoing remarks. Specifically, Applicants point out that the claims all now recite only ligands and coactivator molecules referenced in the instant specification.

Rejections under the enablement requirement of 35 U.S.C. § 112(¶1)

Sufficiency of the Specification

Under the aegis of rejections under the enablement requirement of 35 U.S.C. § 112(¶1), he Examiner has made various allegations concerning the sufficiency of the specification, which Applicants now rebut.

In particular, the Examiner alleges that "[c]learly, the specification is confusing and evasive with regard to the exact amino acid sequence, which has been crystallized". Applicants regret the Examiner's choice of words. Applicants do acknowledge that the subject matter to hand is not straightforward, but suggest that it is susceptible to comprehension and in particular reject any contention that there has been an attempt to be evasive. In fact, the exact amino acid sequence that was crystallized, and whose coordinates are in Appendix 1, is given on page 37, lines 4-5: it is a complex of DES with residues 297-554 of the hERα-LBD, further complexed with the peptide fragment of GRIP1 having SEQ ID NO:4. The fact that the referenced portion of hERα has 258 residues, but only 245 are shown in Appendix 1 is because, during structure refinement of the crystal structure, not all residues were resolved. This fact is discussed at length in the specification as filed, page 39, lines 21-23.

Furthermore, the Examiner makes detailed comments regarding the various sequences found in the Sequence Listing and the structures in the Appendices, as follows:

> [T]he examiner made the unsupported assumption about the protein that had been crystallized, *i.e.*, Met-Asp-Pro fused to the N-terminus of the ligand-binding domain of residue 297-554 containing 361 amino acid residues. Appendix I [*sic*] contain [*sic*] atomic coordinate [*sic*] for 345 residues and no mentioning of the missing residue [*sic*] in the application to be found. The 244 amino acid residues polypeptide of SEQ ID NO: 27 contains a deletion mutation, when compared to the wild-type human binding domain. Similarly, SEQ ID NO: 28 appears to be identical to SEQ ID NO: 27 except that 9 undefined amino acid residues are inserted following Phe-157.

Applicants appreciate the Examiner's attention to such details and are concerned that he has not, in all cases, appreciated various subtleties of the disclosure. Accordingly, Applicants now take the opportunity to explain the disclosure in an effort to give the Examiner a chance to better understand it, and thereby to advance prosecution.

First, Applicants assume that the Examiner's references to peptides having 361 and 345 residues are typographical errors and that respectively 261 and 245 residues are meant. Second, regarding the supposedly "missing residues" from Appendix 1, as explained hereinabove, the specification references the fact that, during refinement of crystallographic coordinates, not all residues were resolved. (See, *e.g.*, specification at pages 38-39, in particular page 39 and lines

21-22). Third, Applicants acknowledge the Examiner's reference to SEQ ID NO: 27 having a "deletion mutation" but ask for further explanation of the relevance of this fact. Finally, the Examiner's comparison of SEQ ID NO's 27 and 28 is accurate and is consistent with the specification (page 39, lines 21-22) and Appendix 1 itself. The disclosure is entirely self-consistent in pointing out that, during structure refinement, 9 amino acid residues in one ERα LBD monomer in the dimer (whose coordinates are shown in Appendix 1) were unresolved. The PDB file in Appendix 1 shows this as a gap in residue numbers between 461 and 470 (specification at page 115). For completeness, Applicants also now point out that, although crystallization took place with a GRIP1 peptide having sequence SEQ ID NO:4, the crystal structure in Appendix 1 shows two instances of the peptide but without resolving the full amino acid sequence in each case. This fact is referenced in the specification at page 42, lines 15-17.

Accordingly, while Applicants acknowledge that there are many intricacies to the subject of protein crystallography, Applicants are keen to point out that there has been no attempt at evasion, as cast by the Examiner. Indeed, it actually seems as if the Examiner has quite shrewdly ascertained various details of the disclosure and therefore is well-positioned to appreciate Applicants' arguments.

Rejections of the Claims

The Examiner has rejected claims 44-48, 50, 136-139, and 142-154 as allegedly "failing to comply with the enablement requirement." The essence of the Examiner's contention is that the amount of experimentation required to practice Applicants' claimed invention is "undue", in particular the exact crystallization conditions. Applicants respectfully traverse the rejection and, also, respectfully draw the Examiner's attention to the claim amendments presented herein.

First, Applicants point out that the Examiner's arguments regarding uncertainties in experimental conditions required for crystallization cannot properly be applied to the isolated and purified complexes recited in claims 136, 137, 139, 148, and 153 as amended herein. Such complexes are do not require crystallization conditions to be made, and therefore enablement of such claims is not dependent on any crystallization description. Accordingly, if the Examiner

continues to maintain that these claims are not fully enabled, Applicants respectfully request that he articulate a specific rejection thereof, supported by its own independent reasoning.

Second, regarding claims 44, 46, 50, 142, 144-147, 150, and 155, the Examiner states that "Applicants have presented no evidence or, indeed, any arguments to establish the adequacy of the disclosure to enable the scope of the instant claims." Applicants respectfully disagree and, at the very least, ask the Examiner to consider carefully the remarks presented in the March 9, 2005 Response, and the claim amendments presented herein. In essence, Applicants have provided good reasons to suggest that, all things considered, the specification is enabling for the rather limited class of complexes contemplated. For instance, given a small number of crystallography techniques customarily deployed in the art as of Applicants' filing date (see article by Gilliland and Ladner, attached hereto, at pages 598-600), Applicants have shown success with one such technique.

Given also the fact that the complexes claimed are all ternary complexes of the ligand binding domain of receptors from the same family, with one of a limited class of agonist ligands, and one of a limited class of coactivator molecules, the expectation that one of ordinary skill in the art may have that Applicants' disclosed conditions would work for other complexes similar to those exemplified would be high. This point is borne out, independently, in the journal article: Gilliland and Ladner ("Gilliland", a copy of which is attached hereto). On page 595 of Gilliland (in the Introduction), it is stated that: "Establishing the correct conditions for the crystallization of a particular biological macromolecule is an empirical process that typically uses techniques and reagents that have proven successful in other cases." This point is further reiterated at page 600, left-hand column, of Gilliland. This shows that it was customary in the art at the time of filing the instant application to look to established successful crystallization protocols as a starting point for a new crystallization. Thus, in the instant situation, where Applicants have described a successful protocol that they have devised, the amount of experimentation to be engaged in by one of ordinary skill in the art to crystallize other complexes falling within the scope of the claims is not expected to be undue. As a specific example, the inventors themselves have achieved crystallization of a similar ERα complex, with a GRIP1 peptide fragment and the

agonist ligand THC, under similar conditions to those deployed in the instant specification. *See*, Shiau *et al.*, *Nature Structural Biology*, 9(5), 359, (2002), at page 363, right-hand column. (A copy of this article is also attached hereto.)

Third, as articulated in the March 9, 2005 Response (page 35, first complete paragraph), the Examiner's assertion that the field is complex (First Office Action, pages 5-6) undercuts the idea that the experimentation involved would be undue. In fact there is legal authority that holds otherwise: "the fact that experimentation may be complex, …, does not necessarily make it undue, if the art typically engages in such experimentation." *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, at 1174 (ITC, 1983). In the instant situation, the Examiner acknowledges that "several crystallization methods for proteins are known in the prior ad [*sic*] and the skill of the artisan are [*sic*] developed" (First Office Action at page 5, bottom). Thus, it follows that those skilled in the art would appreciate how to practice Applicants' claimed invention, notwithstanding the fact that experimentation in that art is frequently complex.

Nevertheless, and notwithstanding the foregoing arguments, Applicants herewith amend claim 44 to recite a complex in which the coactivator is GRIP1 or a peptide fragment thereof having a NR-box motif, and in which the ligand is selected from just the group listed in the specification. Such an amendment reduces much of the scope objected to by the Examiner, and also reduces much of the alleged experimental uncertainty in obtaining crystal structures. Thus, the Examiner's central objection that the claim(s), prior to amendment, had read upon crystals based on "*any* ligand" and "*any* coactivator" is hereby vitiated.

Finally, as with the rejections under the written description requirement of the same paragraph, the Examiner's rejections under the enablement requirement of 35 USC § 112 (first paragraph) take no account of the varying scope of Applicants' claims and are phrased as if only to consider the limitations of independent claims 44 and 136 even though they are applied to all claims under consideration. Nowhere has the enablement of the various claims depending from claims 44 and 136 been separately and individually addressed. Applicants respectfully submit that the rejections of record cannot apply with equal force to all of the claims and therefore such dependent claims can only stand rejected as being dependent upon a rejected base claim, and not

otherwise on the merits, without some clearly articulated reasoning why claims of successively narrowing scope are not enabled. Therefore, on this basis, Applicants respectfully request removal of the rejections at least as they apply to claims 45-48, 50, 137-139, and 142-154.

Rejections under 35 U.S.C. § 112 (¶ 2)

The Examiner has rejected claims 44-48, 50, 138, 142-147, 149, and 152 under 35 U.S.C. § 112 (second paragraph) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants again respond to the Examiner's itemized points as follows.

(a) Claim 44 has been rejected as allegedly indefinite for reciting the phrase "a portion of an estrogen receptor [ligand] binding domain". Applicants note that claim 44, as amended herein, no longer recites the term "a portion of."

With regards to the term "binding domain", Applicants respectfully point out that it is unclear from the second paragraph of Page 5 of the Second Office Action whether the Examiner still objects to this term. If he does, Applicants invite him to reconsider Applicants' description at page 36 of their March 9, 2005 Response.

(b) The Examiner has objected to the term "derivative thereof" in claim 48 and has dismissed Applicants' reference to the specification as filed, at page 26, line 24. Applicant fails to see how the term "NR-box amino acid sequence or derivative thereof" in the claim is materially different from "derivatives of NR-box sequences" in the specification, but in an effort to facilitate the progress of prosecution, have cancelled claim 48 with the amendment herein and have not reintroduced the term elsewhere to other claims.

(c) The Examiner has rejected claims 138 and 143 for referencing "GRIP1", and claims 149 and 152 for referencing "o,p-DDT." Although claims 138, 143, 149, and 152 have been cancelled by amendment herein, the terms GRIP1 and o,p-DDT appear by amendment in other pending claims.

The Examiner appears to have accepted Applicants' definition of the term "GRIP1" ("Glucocorticoid Receptor Interacting Protein 1"), presented in the March 9, 2005 Response.

Nevertheless, the Examiner still requests that Applicants amend claims 138 and 143 to insert "SEQ ID NO: 4" for GRIP1. This amendment would not be proper and, accordingly, Applicants decline to so amend the referenced claims. Instead, Applicants amend claims 138 and 143 to more faithfully track the references in the specification (see, *e.g.*, page 40, at line 31). GRIP1 is a protein; various fragments of GRIP1 have been disclosed in Applicants' specification (*e.g.*, SEQ ID NO:4); such fragments can bind to an estrogen receptor if they have a NR-box sequence (also described in Applicants' specification).

Regarding "o,p-DDT", the Examiner comments that no definition is provided in the specification. Applicants remind the Examiner that there is no obligation to explain to one of ordinary skill in the art what he already knows. o,p-DDT is an isomer of the well-known bis-phenyl compound, DDT, both of whose structures would be well known to one skilled in the art of estrogen receptor studies. Accordingly, a reference to the compound by abbreviated name is sufficient.

Accordingly, Applicants believe that all aspects of the rejection under 35 USC § 112 (second paragraph) have been addressed, either by amendment herein or by remarks previously presented, and respectfully request that the rejection of record of claims 44, 46, 50, 139, 142, and 144–147 be removed.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 136 and 137 under 35 U.S.C. § 102(b) as allegedly being anticipated by Heery, *et al.*, *Nature*, 387:733–736, (1997), ("Heery", hereinafter). Applicants again respectfully traverse the rejection.

The Examiner considers that Heery discloses Applicants' claimed complexes attached to glass beads. Notwithstanding Applicants continued disagreement with such a conclusion, but in an effort to expedite prosecution, Applicants amend claim 136 to recite "[a]n isolated and purified protein complex *consisting of*" three components. Such claims cannot read on a combination of the three recited components attached to some other component such as a glass bead.

Applicants also disagree that their remarks presented in their March 9, 2005 Response are interpreted to mean that 'purified' as recited in the claim means 'purified to homogeneity'. Nevertheless, it is believed that the instant amendment renders such considerations moot.

Accordingly, Heery does not anticipate Applicants' claims 136 and 137 and Applicants respectfully request that the rejection of record be removed.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the subject application is in good and proper order to proceed to issue. If, in the opinion of the Examiner, a telephone conference would resolve any outstanding matters not heretofore resolved, the Examiner is encouraged to call the undersigned at (650) 839-5070.

No fee is believed owed in connection with filing of this amendment. Nevertheless, should the Commissioner determine otherwise, he is authorized to charge any underpayment or credit any overpaymen to Applicants' Deposit Account No. 06-1050 (reference 19459-006US1).

Respectfully submitted,

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Exhibits
Accompanying Amendment and Response under 37 C.F.R. § 1.111
Mailed February 15, 2006

Inside cover page, bibliographic data page, and page 308, of *The Nuclear Receptor Facts Book*, Laudet and Gronemeyer, AP, 2002.

Shiau, *et al.*, "Structural characterization of a subtype-selective ligand reveals a novel mode of estrogen receptor antagonism", *Nature Structural Biology*, 9(5):359–364 (2002).

Gilliland and Ladner, "Crystallization of biological macromolecules for X-ray diffraction studies", *Curr. Op. Struct. Biol.*, 6: 595-603, (1996).